REMARKS

Following entry of the foregoing amendments, claims 1, 38, 40, and 58 will be pending in this application. Claims 1 and 58 have been amended, and claims 2 to 11, 14, 15, 17, 19, 24, 30 to 34, 57, 59, and 60 have been canceled, herein, without prejudice. No new claims have been added. Support for the amendments is found throughout the specification as originally filed, including, for example, Example 3, page 82, line 19 to page 83, line 14, and the amendments thus do not introduce new matter into the application.

Applicant respectfully requests reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Anticipation

Claims 1 to 7, 9, 10, 14, 15, 17, 19, 24, 30, 38, and 40 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. patent application number U.S. 2003/0143732 ("the Fosnaugh application"). To the extent that the rejection applies to the claims as amended herein, applicant respectfully requests reconsideration and withdrawal thereof because the Fosnaugh application fails to teach or suggest every limitation of the amended claims.

The present claims recite compositions comprising two oligomeric compounds in which the first oligomeric compound comprises at least one 2'-fluoro modified nucleoside. The second oligomeric compound comprises at least one nucleoside comprising an inosine base, and at least one of the nucleosides comprising an inosine base is the 3'-terminal hybridizing nucleoside of the second oligomeric compound. The 5'-terminal hybridizing nucleoside of the second oligomeric compound comprises a guanine or cytosine base. Significantly, the Fosnaugh application fails to teach or suggest compositions that comprise such oligomeric compounds. For example, the Fosnaugh application describes small interfering RNA (siRNA) molecules that comprise sense and antisense regions.[1] The application states that the sense and antisense regions can include chemically modified nucleosides, such as 2'-fluoro modified nucleosides and nucleosides having universal bases.[2] "Universal bases" are defined to include C-phenyl, C-naphthyl and other aromatic

[1] Paragraph 13.
[2] Paragraphs 19 and 20.

derivatives, inosine, azole carboxamides, and nitrazole derivatives such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole.[3] The application more specifically teaches that the antisense region can comprise one or more 2'-deoxy-2'-fluoro modified pyrimidine nucleosides,[4] and the 3'-terminal nucleotide overhangs of the siRNA molecules can comprise one or more universal base ribonucleotides.[5] The application does not describe, teach, or suggest, however, siRNA molecules in which the antisense strand comprises at least one 2'-fluoro modified nucleoside, the 3'-terminal hybridizing nucleoside of the sense strand comprises an inosine base, and the 5'-terminal hybridizing nucleoside of the sense strand comprises a guanine or cytosine base. The Fosnaugh application thus fails to teach or suggest every limitation of the present claims, and, therefore, fails to anticipate the claimed subject matter. Applicants accordingly, respectfully request withdrawal of the rejection.

Alleged Obviousness

Claims 1 to 11, 14, 15, 17, 19, 24, 30 to 34, 38, 40, and 57 to 60 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Fosnaugh application in view of U.S. patent number 6,025,140 ("the Langel patent") and U.S. patent number 6,414,127 ("the Lin patent"). To the extent that the rejection applies to the claims as amended herein, applicant respectfully requests reconsideration and withdrawal thereof because the cited references fail to teach or suggest every limitation of the present claims.

To establish *prima facie* obviousness, the Patent Office must demonstrate that the cited prior art reference or combination of references teaches or suggests all the limitations of the claims. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). The Office must also identify "an apparent reason to combine the known elements *in the fashion claimed by the patent at issue*. To facilitate review, this analysis should be made explicit." *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (emphasis added)(citing *In re Kahn*, 441, F.3d 977, 988 (Fed. Cir. 2006)).

[3] Paragraph 129.
[4] Paragraph 19.
[5] Paragraph 20.

As discussed above, the present claims recite compositions comprising two oligomeric compounds in which the first oligomeric compound comprises at least one 2'-fluoro modified nucleoside. The second oligomeric compound comprises at least one nucleoside comprising an inosine base, and at least one of the nucleosides comprising an inosine base is the 3'-terminal hybridizing nucleoside of the second oligomeric compound. The 5'-terminal hybridizing nucleoside of the second oligomeric compound comprises a guanine or cytosine base. Significantly, none of the references cited in the official action, when considered individually or in combination, teaches or suggests oligomeric compounds that comprise nucleosides modified in the fashion presently claimed.

As also discussed above, the Fosnaugh application describes small interfering RNA (siRNA) molecules that comprise sense and antisense regions and states that the antisense region can comprise one or more 2'-deoxy-2'-fluoro modified pyrimidine nucleosides. The application further states that the 3'-terminal nucleotide overhangs of the siRNA molecules can comprise one or more universal base ribonucleotides. The application does not describe, teach, or suggest, however, siRNA molecules in which the antisense strand comprises at least one 2'-fluoro modified nucleoside, the sense strand comprises at least one inosine base-containing nucleoside, one of the inosine bases is located at the 3'-terminal hybridizing nucleoside of the sense strand, and the 5'-terminal hybridizing nucleoside of the sense strand comprises a guanine or cytosine base.

The Langel and Lin patents also fail to describe or suggest such oligomeric compounds. For example, the Langel patent describes peptide-nucleic acid analog conjugates and teaches that the nucleic acid analog moiety of the conjugates can contain various modifications, including modified sugars, modified internucleoside linkages, modified nuclebases, and modified 5' and 3' ends.[6] The patent, however, fails to describe or suggest compositions comprising oligomic compounds that have the claimed pattern of chemical modifications. The Lin patent also fails to describe or suggest the claimed oligomeric compounds. Rather, the patent describes pyrimidine base derivatives known as "G clamps," but fails to describe or suggest oligomeric compounds that are modified in the fashion presently claimed.

[6] Columns 11 to 14.

The cited references thus fail to teach or suggest compositions comprising oligomeric compounds having the modifications presently claimed, and there is no reason why those of ordinary skill in the art would have produced oligomeric compounds having the particular pattern of claimed modifications prior to applicant's invention. Significantly, applicant surprisingly discovered that oligomeric compounds comprising the claimed pattern of modified nucleosides exhibit superior inhibition of target RNA expression. As indicated in experimental Example 3, siRNA molecules in which each nucleoside of the sense strand contains a 2'-fluoro modification and the antisense strand contains an inosine base at the 3' terminal hybridizing nucleoside and a cytosine base at the 5'terminal hybridizing nucleoside[7] inhibited expression of PTEN mRNA to a significantly greater extent than did siRNA molecules having different patterns of chemical modifications. Notably, none of the cited references, when considered individually or in combination, describes or suggests that oligomeric compounds modified in the fashion presently claimed would have such unexpected and advantageous inhibitory activity. Moreover, the Office has failed to identify any reason why those of ordinary skill in the art would have designed oligomeric compounds having the particular modifications recited in the present claims. (To establish *prima facie* obviousness, the Office must identify "an apparent reason to combine the known elements *in the fashion claimed by the patent at issue*. To facilitate review, this analysis should be made explicit." *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (emphasis added)(citing *In re Kahn*, 441, F.3d 977, 988 (Fed. Cir. 2006)).

Compositions comprising oligomeric compounds having the claimed pattern of chemical modifications thus would not have been obvious to those of ordinary skill in the art at the time of the invention, and applicant accordingly, respectfully requests withdrawal of the rejection for alleged obviousness.

[7] siRNA constructs containing oligonucleotide 279471 in the antisense strand and oligonucleotide 271387 in the sense strand.

Conclusion

Applicant believes that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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